IM INTERNAL MEDICINE
FOR THE SPECIALIST

Diagnosis and Management of Organophosphate Poisoning

By Michael J. Hodgson, M.D.

Organophosphates can be extremely toxic in minute amounts, and prompt recognition of symptoms secondary to acute exposure can be life-saving. The newer techniques of diagnosis, several forms of recently described presentations, emerging neurotoxicity considerations, and the available resources for emergency information on diagnosis and treatment are presented in this article.

In the past, poisoning from organophosphate pesticides was considered a disease of farmers and migrant workers, of suicidal intent, or, rarely, of accidental community exposures. Cases have been documented more recently of poisoning from acute and chronic ingestion outside the workplace, and occupational inhalation exposures outside the farming industries. For example, the Environmental Protection Agency (EPA) had more than 1,000 cases of residential poisoning in its Pesticide Incident Registry, a listing of suspected pesticide intoxication episodes, while it was still active. The vast majority of these were poorly documented and therefore of little use, either for research or clinical purposes.

Although awareness of exposure hazards has increased among primary-care physicians, and the suspicion of pesticide intoxication often arises, newer methods of diagnosis and exposure confirmation may not generally be known. Incidents may, therefore, continue to be documented inadequately. This article addresses the newer techniques of diagnosis, several forms of recently described presentations, emerging neurotoxicity considerations, and available resources for emergency information on diagnosis and treatment.

Dr. Hodgson is Assistant Professor of Medicine, Occupational Medicine Program, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

REVIEW: MECHANISM OF ACTION, PHYSIOLOGY, AND TOXICITY

The mechanism of organophosphate toxicity is based on the ability to block the enzyme acetylcholinesterase, leading to the accumulation of acetylcholine. Initially, the blockage is reversible, but phosphorylation soon leads to irreversible binding ("aging"). Recovery requires the generation of new enzyme. Absorption may occur through inhalation or ingestion, or percutaneously. Some individuals are at higher risk for actual poisoning because of their naturally lower levels of acetylcholinesterase. It is possible to induce secondary cases of poisoning during the treatment of organophosphate toxicity through heavy contact when treating individuals with contaminated excreta.

Acetylcholine is the neurotransmitter in a variety of synapses: postganglionic parasympathetic nerves, preganglionic nerves of the para and sympathetic systems, smooth muscles, and in portions of the central nervous system. The in-

TABLE I

SYMPTOMS FROM ORGANOPHOSPHATE POISONING

Receptor	Organ	Symptoms
Nicotinic	Muscles	Easy fatigue Twitching/fasciculation
	Autonomic ganglia	Tachycardia Hypertension Hyperglycemia
Muscarinic	Heart	Bradycardia
	Smooth muscles	Increased peristalsis with diarrhea and cramps, nausea, vomiting
		Increased bladder tone with incontinence and frequency
		Miosis (mydriasis may occur subsequently) Chest tightness and wheezing
Central nervous system "neurotoxic esterase"		Dizziness Weakness Headache Acute psychosis (mania) Ataxia Seizures Sleep and dream disturbances
Delayed neurotoxicity	Axon	Peripheral neuropathy symptoms

duced symptoms are the result of increased synaptic transmission in those sites. Manifestations include not only nonspecific symptoms like fatigue, muscle weakness, and headache but also symptoms related to specific sites of action, such as muscle twitching, abdominal cramps, and diarrhea. Specific signs include bradycardia, diarrhea, diaphoresis, lacrimation, and salivation. These symptoms and signs may occur as early as two hours and as late as 12 hours after absorption. Table I lists symptoms by their specific mode and site of action.

Atropine can protect against the nicotinic but not against muscarinic or central-nervous-system (CNS) effects. The mechanisms for the CNS symptoms and of neuropathic complications are not well understood. Electroencephalographic changes after exposure and psychoses have been described in production workers. Such CNS symptoms are commonly attributed to "neurotoxic esterases," a poorly defined group of possibly several hundred enzymes in the brain. No large systematic surveys have been published that would allow a reliable delineation of the frequency distribution of individual symptoms. Nonetheless, it has become clear that symptoms may persist for several months, even after normalization of cholinesterase levels.

DIAGNOSIS

The diagnosis of organophosphate poisoning generally requires a high degreee of suspicion.

The occurrence is not thought to be frequent, but no reliable statistics are available. Signs and symptoms may be vague and nonspecific rather than the commonly expected parasympathetic signs and symptoms. Intoxication has been mistaken for psychosis, a chronic fatigue syndrome, gastrointestinal illness or flu, and upper-respiratory-tract infections. Patients provide the necessary information only when practicing physicians ask basic questions about exposures at work and home and harbor a marked degree of suspicion. Common organophosphate exposures involve commercial pesticide application, farm work (vegetable and fruit picking), and recent application of pesticides at home or work. One recent large outbreak has been attributed to ingestion of watermelon contaminated with an organophosphate. Although treatment should not await laboratory confirmation in severe cases, the diagnosis should be confirmed. Diagnostic confirmation with one of the methods below is usually necesssary to convince employers, contractors, or the patients themselves that their episode was preventable and should not recur. Only if the work practice or setting leading to the poisoning incident is identified, can subsequent reexposure be prevented.

The normal range of red-cell and serum cholinesterase levels is so broad that values may decrease to almost one-half their original level and still be within normal limits. It is, therefore, difficult to make the diagnosis of organophosphate poisoning on the basis of one blood or serum cholinesterase level alone. In the occupational setting, where exposure may be predictable, it is standard practice to obtain serial determinations of red-blood cell and serum cholinesterase. This is, in fact, law in the state

of California for pesticide applicators. When levels decrease by 25 percent, individuals are removed from exposure. In several recently published incidents, such prospective determinations had not been undertaken because the affected groups were not covered by mandatory surveillance provisions. Nevertheless, the diagnosis of poisoning could be made through subsequent rises in cholinesterase levels.

One must distinguish between red-cell ("true") and serum ("pseudo") cholinesterase level determinations. The latter are generally assumed to return to normal more rapidly. Red-cell cholinesterase levels cannot be regenerated from within the red cell, because the appropriate enzymes are missing and must await marrow replacement of the red-cell pool. This physiological difference may be used in one of the diagnostic techniques.

Organophosphate poisoning does not occur in a legal vacuum. Most employers are unwilling to acknowledge the presence of work-related disease in the absence of objective findings implicating a specific agent. Immediate and long-term costs of the illness must be borne by the patients, unless their disease was induced by a second party. Documentation of poisoning and of the compound may therefore be appropriate. Three different diagnostic strategies are available, for three different purposes: (a) immediate emergency treatment, (b) likely exposure assessment, and (c) documentation of the specific agent. Three courses of action are available, none of which precludes the others.

Therapeutic Trial with Atropine. In the acute setting, with a high degree of clinical suspicion, treatment should be initiated after drawing a first blood sample without awaiting confirmation of cholinesterase levels. The response to therapy will provide an answer at least to the question of symptom etiology in many cases.

Monitoring of Urinary Metabolites / Excretion. Urine may be collected for 24 hours for various metabolites (i.e., the leaving or the alkyl groups.) The various leaving groups allow identification of specific substances. Collection must begin early to be successful; in general, the first 24-hour urine is collected. Information on which components should be ordered may be obtained from either the Pesticide Information Hotline in Atlanta [(800) 858-7378] or the New Mexico Poison Control Center [(505) 843-2551]; both are

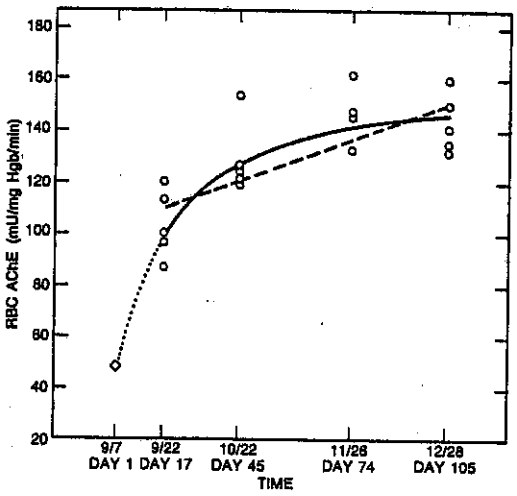

Figure 1. *Change in erythrocyte cholinesterase levels over time. RBC AChE: erythrocyte cholinesterase level in mU/mg HgB/min; normal range: 100 to 220 mU/mg HgB/min.* (Reproduced with permission, from Hodgson MJ et al *J Occupat Med 28 (6):* 434, 1986)

available 24 hours a day and are funded by the EPA as nationwide resources.

Temporal Course of Red-Cell Cholinesterase Level Recovery. The course of cholinesterase levels may be followed over time. Serial determinations of cholinesterase levels will reveal a gradual increase over time. The rate of increase changes over time and seems to follow an exponential course. One such course, documented in office workers, is plotted in Figure 1. The exponential models fit this distribution of data points much more precisely than did other distributions. Several other poisoning episodes have demonstrated such patterns of recovery. Whether the slopes of such recovery are similar for different compounds is unknown.

The earlier a first level is obtained, the greater is the likelihood of detecting changes. Obviously, this strategy requires knowledge of the laboratory's precision. Changes of up to 10 percent are common in one individual over time. If an increase approaches 10 percent between a first and a second level, a third level should be drawn. The ideal frequency of measurements has not been determined. For serum cholinesterase it is at least weekly, although more frequent determinations may eventually allow more accurate diagnosis. For red-cell cholinesterase levels, the optimal frequency is more likely to be weekly or biweekly, as the increase occurs at a slower pace.

It is well known that some organophosphates lead to clinical toxicity later and require treatment for longer periods of time after ingestion than do others. As they are known to have varying degrees of lipid solubility, speed of redistribution to and reuptake from fatty tissue differs for each compound. Various organophosphates may then lead to different temporal patterns of recovery in red-cell cholinesterase levels over time, at least in part because of redistribution of the active agent from an inaccessible body compartment, such as fat to the bloodstream.

TREATMENT

The treatment of choice is the intravenous administration of atropine. A less desirable alternative is intramuscular administration. Although atropine does not regenerate the enzyme or block the nicotinic effects, it is useful in the acute management of poisoning. Adequate treatment is established through the documentation of atropinization: development of tachycardia (pulse of 140 beats per minute), pupillary dilatation, and exsiccation of the mucous membranes. Recurrence of bradycardia, lacrimation, salivation, rales, and miosis are indicative of inadequate atropinization. Atropine must often be administered in 15-minute intervals in order to maintain an adequate therapeutic effect. Adults generally receive 0.4 to 2.0 mg, whereas children under the age of 12 receive 0.05 mg per kg of body weight in 15-minute intervals until atropinization is achieved. Severely poisoned individuals may require substantially greater doses (two- to threefold).

Pralidoxime is generally administered in cases

of severe poisoning. It may actually relieve the nicotinic symptoms of toxicity when given within 24 to 36 hours. One gram should be administered slowly (i.e., less than 0.5 mg per minute or in infusions over 30 to 60 minutes).

Patients should be observed for at least 24 hours. If evidence of poisoning or pulmonary edema recur, atropinization must be reinstituted. Signs and symptoms may recur even over one week later. This delay in recovery may be in part due to the redistribution of organophosphate absorbed initially into the fatty tissue and subsequently redistributed into the bloodstream with new development of toxicity.

In cases of mixed poisoning with carbamates, there is some concern that pralidoxime may actually be harmful. If respiratory status worsens during slow, dilute administration of pralidoxime, administration should be discontinued.

NEUROTOXICITY

Organophosphate pesticides are associated with three forms of neurotoxicity. The acute form is attributed to the inhibition of synaptic acetylcholinesterase. It may occur after exposure to any of the compounds. The effects are thought to be reversible and leave no evidence of permanent damage.

A peripheral neuropathy with onset delayed to several weeks after exposure has been described after exposure to a variety of compounds. Histologically, it is characterized by degeneration of the large-diameter axons in the spinal cord and peripheral nerves. Clinically, it is seen as a syndrome of progressive weakness rising from the legs with flaccid paralysis. It reverses only slowly, frequently leaving residual spasticity and paralysis.

The same two steps, phosphorylation and aging, are thought to occur as with the acute organophosphate effects. Not all compounds have been demonstrated to have the potential for inducing the late syndrome. It is uncertain whether the neurotoxicity is due to intersubject variablility (e.g., in cholinesterase levels) or to the agent's characteristics, including direct structure-action relationships or lipid solubility.

An intermediate syndrome was recently described, temporally similar to the acute syndrome, but histologically similar to the delayed syndrome. It seems to occur 24 to 96 hours after absorption of the compound and be associated with axonal damage.

NEWER PRESENTATIONS

Epidemics in communities sprayed with pesticides have been well described. Similarly, those applying the pesticides are known to be at risk, primarily in agricultural field work. On the other hand, organophosphates are used in a large variety of other settings, all with the potential for toxicity. The EPA Pesticide Incident Registry contains many reports of exposure in nontraditional settings, mostly unconfirmed because attempts at diagnosis were not undertaken early enough. A high index of suspicion is required to associate the frequently nonspecific symptoms with exposure. Several recent episodes from the literature are summarized to present the broad range of such incidents.

Residential Episodes. An 11-day-old boy was brought to the San Francisco General Hospital emergency room because of an apneic episode. Because of pinpoint pupils and excessive salivation, pesticide poisoning was considered, and he was treated appropriately. An organophosphate with a long half-life was found on dishtowels, food preparation surfaces, and the infant's clothing (Dunphy 1980).

Following an office visit, five children diagnosed with gastroenteritis were sent home to consume fluids. Over the next 24 hours all worsened and visited the local emergency room. Three of five children were unconscious; classic signs of poisoning were observed. Two fatalities resulted. Organophosphate had been applied eight days before the incident (Dean 1984).

Acute Dietary Exposure. Around July 4, clusters of pesticide poisoning in families were associated with eating striped watermelons. Reports were confirmed in Washington, Oregon, and California. Two-thirds of the identified watermelons tested positive for aldicarb, a carbamate not generally used for watermelons. The mode of contamination could not be clarified (Green 1987).

Chronic Dietary Exposure. Five individuals with chronic gastrointestinal symptoms ranging from several months to two years were seen in an emergency room. Restriction of vegetable and

fruit components of a diet and serial determinations of cholinesterase levels allowed attribution of chronic symptoms to organophosphate poisoning (Ratner 1983).

Office Workers. Five office workers developed symptoms compatible with organophosphate poisoning after their office was sprayed during occupancy. Serial red-cell cholinesterase determinations allowed attribution of their symptoms to poisoning (Hodgson 1986).

Asthma. In addition to their cholinesterase-mediated effects, organophosphates may also induce hypersensitivity. Two cases of asthma inadequately controlled with aminophylline and aerosols and with albuterol and cromolyn sodium were attributed to organophosphates. The individuals showed specific reactions when challenged with organophosphates. The reactions could be blocked with prednisone but not with atropine (Bryant 1985).

SUGGESTED READING

Background reading and reference books

1. Hayes WJ: *Pesticides Studies in Man.* Williams and Wilkins, Baltimore, 1982
2. Morgan DP: *Recognition and Management of Pesticide Poisoning (3rd ed.), US Government Printing Office: EPA-540/9-80-005, 1982*

Reviews of neurotoxicity

1. Cherniack MG: Toxicological screening for organophosphorous-induced delayed neurotoxicity: Complications in toxicity testing. *Neurotoxicology, 1988* (in press)
2. Barrett DS, Oehme FW: A review of organophosphorus ester-induced delayed neurotoxicity. *Vet Hum Toxicol 27:* 2237 1985

Recent clinical descriptions

1. Bryant DH: Asthma due to insecticide sensitivity. *Aust NZ J Med 15:* 66, 1985
2. Coye MJ et al: Clinical confirmation of organophosphate poisoning of agricultural workers. *Amer J Ind Med 10:* 399, 1986
3. Coye MJ et al: Clinical confirmation of serial organophosphate poisoning by serial cholinesterase analyses. *Arch Int Med 147:* 438, 1987
4. Dean A et al: Organophosphate pesticide poisoning among siblings—Mississippi. *MMWR 33:* 592, 1984
5. Dunphy J et al: Pesticide poisoning in an infant—California. *MMWR 29:*329, 1980
6. Hodgson MJ et al: An outbreak of organophosphate poisoning in office workers. *J Occ Med 28:* 434, 1986
7. Midtling JE et al: Clinical management of field worker organophosphate pesticide poisoning. *West J Med 143:* 514, 1985
8. Ratner D et al: Chronic dietary anticholinesterase poisoning. *Israel J Med Sci 19:* 810, 1983
9. Green MA et al: An outbreak of watermelon-borne pesticide toxicity. *Amer J Publ Health 77:* 1431, 1987